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by Retno Sari

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Enhancement of solubility and dissolution rate of quercetin with solid dispersion system formation using hydroxypropyl methyl cellulose matrix

Dwi Setyawan, A. Ahmad Fadhil, Dayanara Juwita, Helmy Yusuf, Retno Sari

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, Surabaya, East Java, Indonesia

Corresponding Author:
Dwi Setyawan, Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, Surabaya, East Java, Indonesia.
E-mail: dwisetyawan-90@ff.unair.ac.id

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ABSTRACT

Objective: The aim of the present study was to obtain raw quercetin materials using solid dispersion (SD) system with higher solubility and dissolution rate than pure quercetin. **Materials and Methods:** The SD of quercetin-hydroxypropyl methyl cellulose (HPMC) was prepared by solvent method. Subsequently, the SD was tested for its solubility and *in vitro* dissolution. The physicochemical properties were characterized by powder X-ray diffractometer, differential thermal analyzer, FT-infrared spectrophotometer, and scanning electron microscope. **Results:** Solubility test, dissolution test, and physicochemical property characterization on the SD of Quercetin-HPMC were then compared to pure quercetin and the physical mixture. Based on the results of one-way analysis of variance test, $\alpha = 0.05$ indicated a significant difference in the solubility and dissolution rate. **Conclusions:** Quercetin-HPMC SD was in substance which resulted in the increase of solubility and dissolution rate. These findings may enhance bioavailability to increase drug efficacy.

INTRODUCTION

Quercetin has diverse biological effects regarded as beneficial to health, including antioxidants, anticancer, and antivirus. However, quercetin is slightly soluble in water (0.3 mg/mL), as a result, its absorption in oral administration is limited [1,2]. Moreover, solubility and dissolution rate are two of the decisive factors in the absorption process, especially for oral administration. The bioavailability of an active pharmaceutical ingredient with low solubility given orally depends on the dissolution rate of the dosage form [3]. Therefore, many efforts have been performed to improve the solubility and dissolution rate of drug substances, namely, by modifying the physical properties of the ingredients, adding a solubility enhancer, forming new compounds, and solid dispersion (SD) system [4].

In addition, SD is a homogeneous mixture of one or more active ingredients in an inert matrix with the aim of improving oral bioavalibility of poorly soluble drug substances [5]. SD can also be regarded as a dispersion of one or more active substances in an inert carrier or matrix in the solid state. The system is conducted by melting, dissolving, and combining melting and dissolving techniques. Dispersion resulted from melting was often called "melt," an SD system created by dissolution method, called "coprecipitation" or "coevaporation," such as povidone-sulfathiazol and reserpine-PVP. Furthermore, selection of the carrier affects the solubility profile of the dispersed drug substance. The previous study showed that water-soluble carrier produces a rapid release of drug substance from the carrier [6,7].

Hydroxypropyl methyl cellulose (HPMC), a cellulose derivative, is a hydrophilic polymer that can improve the solubility of the crystalline drug. HPMC exhibits a high capability to form a solid solution with poorly water-soluble drugs [8]. It is reported that HPMC with a small viscosity, such as HPMC 3 Cps, are commonly used as a matrix in the SD [8]. Taken together, it is possible that an SD made from quercetin and HPMC 3 Cps can increase the solubility and dissolution rate of quercetine. Thus, the present study focused on the formation of the SD of quercetin-HPMC 3 Cps to improve the dissolution and bioavailability of quercetin.

MATERIALS AND METHODS

Materials

Materials used in this study were quercetin hydrate ($C_{15}H_{10}O_7$. xH_2O; MW: 302,24 g/mol) from Tokyo Chemical Industry Co., Ltd., Japan, Lot 83N_2O; HPMC 2910 (HPMC) 3 cps from Shin Etsu, Japan; ethanol(E-Merck, Germany); citric acid, sodium hydroxide, and potassium bromide pro infrared spectroscopy (Sigma-Aldrich, Germany).

Methods

Preparation of physical mixture (PM) of quercetin-HPMC

PM of quercetin-HPMC were prepared in the ratios of 1:1, 1:2, and 1:3 (w/w) by stirring the mixture slowly in a mortar until homogenous mixture was obtained.

Preparation of quercetin-HPMC SD

SD of quercetin-HPMC was made in the ratios of quercetin: HPMC = 1:1, 1:2, and 1:3 (w/w) by dissolving quercetin and HPMC. The solution was then evaporated at room temperature for 48 h. SD obtained was stored in a desiccator in vacuum condition.

Quercetin Solubility Test

The solubility test on SD of quercetin-HPMC (SD), PM, and pure quercetin (QC) were performed at 30°C ± 0.5°C. Precisely, pure 20 mg of quercetin or the PM and SD with the equivalent amount of quercetin accurately weighed and placed into 40 ml of the media citrate buffer (citric acid - NaOH) pH 5.0 ± 0.5 and stirred using a magnetic stirrer with a circulating water bath for 6 h. Subsequently, 3 ml of the samples were taken and filtered with a 0.45 μm membrane filter. Its absorbance was then measured using ultraviolet (UV)-visible spectrophotometer (Cary 50 Conc.Varian®, San Diego, California, USA), at a wavelength of 366.95 nm.

Quercetin Dissolution Test

The powder samples equivalent to 20.0 mg quercetin were weighed accurately and then placed in a beaker containing 900 ml of citrate buffer (pH 5.0 ± 0.5) with SLS 1%. The samples were stirred in a basket (tipe 1) stirrer at a constant temperature of 37 ± 0.5°C at a speed rate of 100 rpm using dissolution tester (Erweka DT 700, Heusenstamm, Germany). Samples were withdrawn 5.0 ml at 5, 10, 15, 30, 45, 60 min, and equal volumes of fresh dissolution medium were replaced. The solution was then filtered with Whatman filter paper and diluted appropriately. Quercetin was determined by UV-visible spectrophotometer method.

Statistical Analysis

To determine the difference in dissolution profile among the groups, a statistical analysis on the dissolution efficiency (DE) at minute 30 was performed using one-way analysis of variance (ANOVA) test at $\alpha = 0.05$.

Characterization with Differential Thermal Analyzer (DTA)

Thermal analysis of the samples was performed by DTA (Mettler Toledo FP85 TA Cell, Polaris Parkway Columbus, USA) with a calibrated temperature using indium. A volume of 5.0-7.0 mg of the samples was put on a covered aluminum pan. DTA was then performed in the temperature range from 50 to 300°C with a heating rate of 10°C per minute.

Characterization with Powder X-ray Diffraction (PXRD)

PXRD analysis was conducted at room temperature (± 25°C) using diffractometer (Phillips X'Pert, PANalytical, Almelo, Netherlands). Measurement was then performed under certain conditions, involving Cu metal target, Kα filter, voltage 40 kV, and 40 mA electrical current. Analysis was performed in the range of 5-50°.

Characterization with Fourier Transform Infrared Spectroscopy

Dispersion of 1% powder samples was performed in Kalium Bromide (KBr). Infrared spectrum was obtained by infrared spectrophotometer (Spectrum One, Perkin Elmer, Massachusetts, United States) in the wave number range of 400-4000 cm^{-1}.

Characterization with Scanning Electron Microscopy (SEM)

The powder samples were put into an aluminum holder and then coated with gold with a thickness of 10 nm. The samples were then observed at various magnifications using SEM (Jeol JSM-7900F, Tokyo Japan) with 20 kV and 12 mA.

RESULTS AND DISCUSSION

Quercetin Solubility Test

Since quercetin rapidly degraded at pH ≥5, the solubility test was conducted at 5.0 ± 0.5 using citrate buffer [9]. The standard curve of quercetin was made before the quercetin measurement in pure quercetin, PM, and SD. The equation of linear regression obtained from standard curve was $Y = 0.05257 X + 0.00221$ with $r = 0.99979$. The results of solubility test on QC, PM1, PM2, PM3, SD1, SD1, and SD3 were 1.64 ± 0.14; 2.96 ± 1.24; 3.64 ± 0.66; 3.69 ± 0.85; 4.24 ± 0.20; 5.36 ± 0.34 and 5.75 ± 0.01 ($\times 10^{-4}$ % w/v), respectively.

The results of the solubility test showed that the percentage of quercetin dissolved in the media when the SD system applied was increased following the addition of HPMC (Figure 1).

Solubility results of SD system with the ratio of 1:3 demonstrated the highest quercetin solubility. This increase might be due to the formation of molecular dispersion or microstructural dispersion of quercetin in the hydrophilic matrix. The formation of micellar structure with the media might also increase the solubility of quercetin. The formation of micellar structure is also demonstrated by other water-soluble polymers [10].

Quercetin Dissolution Test

The dissolution test results of pure quercetin (QC), PM of quercetin-HPMC (PM) and quercetin-HPMC SD are presented in Figure 2.

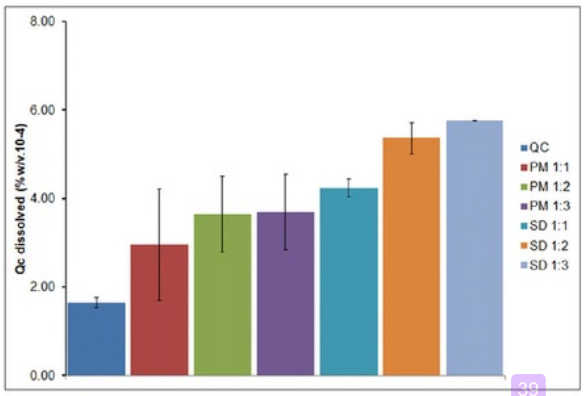

Figure 1: The solubility profile of pure quercetin (QC), physical mixture (PM), and solid dispersion (SD) in citrate buffer media (pH 5.0 ± 0.5) at 30°C ± 0.5°C. Data are the average of the three-time replication ± SD

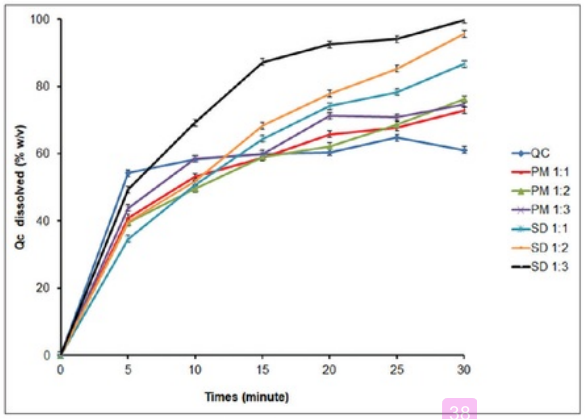

Figure 2: Dissolution profile of pure quercetin (QC), physical mixture (PM), and solid dispersion (SD) in citrate buffer (pH 5.0 ± 0.5) with SLS 1% media at 37°C ± 0.5°C. Data are the average of the three-time replication ± SD

The results of DE at minute 30 (DE_{30}) [11] showed that the SD of quercetin-HPMC (SD) with the ratio of 1:3 had greater dissolution rate than the pure quercetin (QC). To determine the difference in dissolution profile among the groups, a statistical analysis on the DE_{30} was performed using one-way ANOVA test at $\alpha = 0.05$. The results of one-way ANOVA test followed by Tukey's post-test using IBM SPSS statistics ver 23 indicated that there are significant differences in DE_{30} among the groups at confidence level of 0.95 ($\alpha = 0.05$).

The average DE_{30} indicated that all systems had greater value than pure quercetin. The DE_{30} showed that QC < PM (1:1) < PM (1:2) < PM (1:3) < SD (1:1) < SD (1:2) < SD (1:3).

In the dissolution profile, the SD system of quercetin-HPMC with the ratio of 1:3 showed the highest dissolution rate as compared to the other systems.

The dissolution study showed that quercetin has the lowest dissolution profile might be due to its hydrophobic

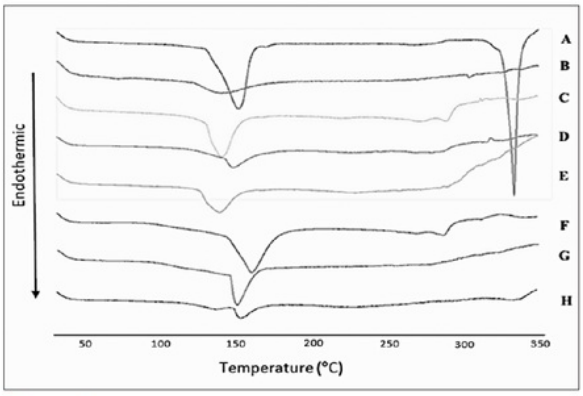

Figure 3: The differential thermal analyzer thermogram of QC (A), hydroxypropyl methyl cellulose (B), physical mixture 1:1 (C), physical mixture 1:2 (D), physical mixture 1:3 (E), solid dispersion 1:1 (F), solid dispersion 1:2 (G), and solid dispersion 1:3 (H)

nature. Consequently, quercetin was difficult to interact with the media. Meanwhile, SD system of quercetin-HPMC with the ratio of 1:3 performed the greatest dissolution profile due to the use of HPMC as carrier. This enhancement in dissolution profile might be due to the capability of HPMC molecule in covering quercetin molecule, thereby increasing wetting process and preventing aggregation of quercetin leading to ability to retain its small particle size. As a result, particle size reduction increased the surface area on the media, led to the increase in the dissolution rate of quercetin in SD system [10]. The increase in the DE may be caused by the reduction in particle size due to the addition of HPMC [11]. It is also suggested that the improved solubility and dissolution that are not too large was caused by a tendency of quercetin molecules to build an intermolecular binding leading to the decrease in homogenous molecule dispersion of quercetin in the media.

Thermal Analysis using DTA

Thermal analysis using DTA was conducted at a temperature range of 50-350°C with a heating rate of 10°C/min. The thermogram of QC, HPMC, PM 1:1, PM 1:2, PM 1:3, SD 1:1, SD 1:2, and SD 1:3 can be seen in Figure 3.

Thermogram DTA (Figure 3) showed the melting peak of the pure quercetin occurred at 325.4°C with enthalpy of 111.0 J/g. Meanwhile, in the DTA thermogram of HPMC, there was a widened endothermic peak around 125°C indicating a glass transition condition [12]. In the PM of quercetin-HPMC with the ratios of 1:1 and 1:2 both endothermic peaks still emerged; however, their melting temperature and enthalpy were smaller than those in the pure quercetin. The DTA thermogram of the SD, moreover, showed that the endothermic peak of quercetin emerged in the SD of quercetin-HPMC with the ratio of 1:1, yet it did not emerge in the SD with the ratios of 1:2 and 1:3. The thermogram of the SD with the ratio of 1:1 also showed that the melting point of the system was 283.8°C with enthalpy of 6.88 J/g.

These results indicate that the quercetin particles in the SD system were still in crystalline form. The shifting of the melting point into a lower point and the decrease in the

enthalpy value indicated by DTA thermogram due to the SD system may decrease bond energy among molecules that eventually reduces the energy required to melt the SD. The decrease and lost of endothermic peak suggests that the quercetin molecules are distributed into the HPMC matrix to form an amorphous dispersion [11].

Analysis using PXRD

The X-ray diffraction analysis was performed using PXRD at the angle ranging from 2θ = 5.0 to 50.0°. The diffractogram QC, HPMC, PM 1:1, PM 1:2, PM 1:3, SD 1:1, SD 1:2, and SD 1:3 were presented in Figure 4.

The results of PXRD test showed the diffraction pattern of quercetin crystalline phase in which the specific interference peaks at angle 2θ were 5.2°, 10.6°, 11.76°, 11.88°, 13.52°, 14.12°, 14,32°, 21.82°, 26,38°, and 27.38° [11].

In the diffractogram of the PM of quercetin-HPMC, all specific peaks of quercetin emerged, indicating that the crystallinity of quercetin remained unchanged in the PM. The diffractograms of the PM of quercetin-HPMC with the ratios of 1:1, 1:2, and 1:3 showed the superposition of quercetin and HPMC diffractograms. The diffractogram of QC-HPMC SD showed decreases in the intensity of several diffraction peaks and the lost of diffraction peaks at 2θ = 5.2 and 11.76. These results demonstrated the changes of crystalline form of quercetin to amorphous form. In agreement with this finding, the changes to amorphous form occur in the SD system using PVP. Moreover, the report suggests that the quercetin is molecularly dispersed in the matrix [11].

Diffractogram intensities showed by the SD system of quercetin-HPMC with the ratio of 1:3 had the lowest value. In general, there was a decrease in the peak intensity of the diffractogram of the SD system as the number of polymers in the system increased.

Analysis using Infrared Spectroscopy Fourier Transform Infrared (FTIR)

The spectrum of infrared spectroscopy of pure quercetin QC, HPMC, PM 1:1, PM 1:2, PM 1:3, SD 1:1, SD 1:2, and SD 1:3 is presented in Figure 5. FTIR spectroscopy has been widely used to examine changes in physical and chemical structures of a material [13]. In the infrared spectrum, the transmission peak of specific aromatic functional groups of quercetin is at a wavenumber of 1522 cm^{-1}, and –OH group will become sharp at a wave of 3411 cm^{-1} [11]. Meanwhile, HPMC has a transmission peak of specific functional groups, C-O-C at a wavenumber of 1062 cm^{-1}, and –OH group will become sharp at a wavenumber of 3467 cm^{-1} [14].

The peaks of the specific transmission of quercetin and HPMC appeared in the spectra of the PM and the SD system at the same wavenumber presented in Figure 5. This indicates that there was no modification or interaction between the drug and the carrier. The spectra of the SD system showed that its transmission peak had widened and shifted at 3300-3500 cm^{-1}, similar to the transmission peak of the pure quercetin (QC). The widening and shifting of the peak

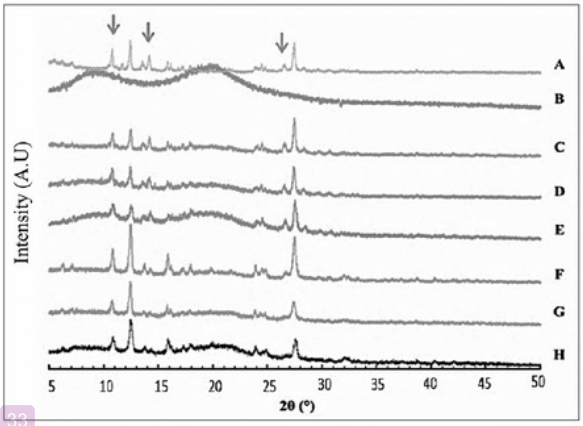

Figure 4: X-ray diffractograms of QC (A), hydroxypropyl methyl cellulose (B), physical mixture 1:1 (c), physical mixture 1:2 (D), physical mixture 1:3 (E), solid dispersion 1:1 (F), solid dispersion 1:2 (G), and solid dispersion 1:3 (H)

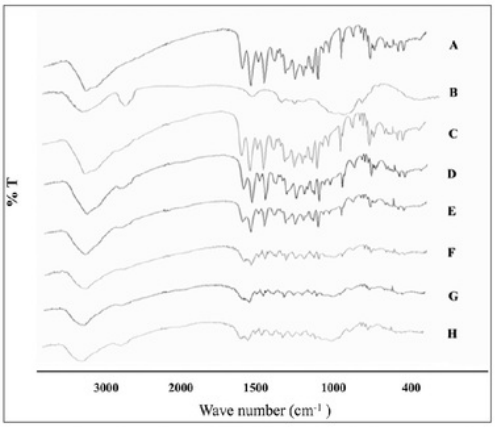

Figure 5: The infrared spectra of QC (A), hydroxypropyl methyl cellulose (B), physical mixture 1:1 (C), physical mixture 1:2 (D), physical mixture 1:3 (E).

indicates that the intermolecular hydrogen bonds are formed between the aglycone phenyl hydrophobic groups of quercetin and the hydroxyl groups of HPMC [10,15,16].

Analysis using SEM Microscopy

The results of morphological habit evaluation of quercetin (QC), HPMC, and quercetin-HPMC solid dispersion system with the ratio of 1: 3 (SD) can be seen in Figure 6.

SEM photomicrographs of raw quercetin demonstrated a non-uniform particle size and needle-shaped particles. This is in agreement with the previous study [10,11]. HPMC showed the prismatic shape and fibrous shape, which support the finding in the previous report [7].

In the micrograph of SD, quercetin emerged in the form of needle crystals dispersed in the carrier, HPMC. Thus, the SD system can be classified as a microcrystalline SD. The crystalline SD system is formed when the rate of the

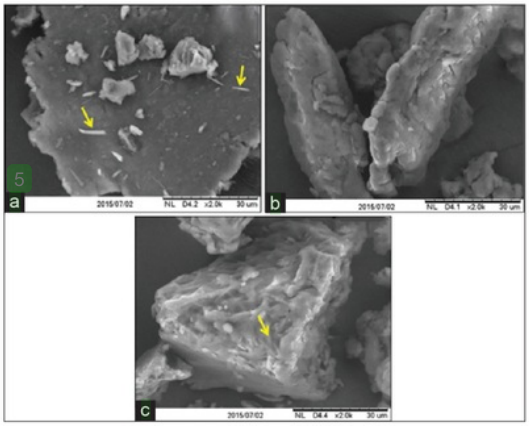

Figure 6: Scanning electron microscopy micrograph of QC (a), hydroxypropyl methyl cellulose (b) and solid dispersion (c) with the ratio of 1: 3 at ×2000 magnification. The arrows indicate the microcrystal quercetin

crystallization is greater than the rate of drug solidification molecularly dispersed in the carrier. There are several mechanisms triggering SD system to enhance the dissolution of drug substance, namely, particle size reduction, reduced interparticle aggregation, damping process from the carrier as well as changes in the physical properties of drugs, such as the degree of crystallinity and amorphous form [16,17].

CONCLUSION

The present study indicates that quercetinin QC-HPMC SD exhibits an amorphous forms due to decrease in crystallinity as compared to the pure quersetin and the PM, which results in the increase of solubility and dissolution rate. These findings may contribute to the improvement of the bioavailability of quercetin to increase drug efficacy.

ACKNOWLEDGMENT

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5